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Evaluation of absorption enhancement for a potent cyclopeptidic alpha(nu)beta(3)-antagonist in a human intestinal cell line (Caco-2).

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Different absorption enhancing principles for a potent cyclopeptidic alpha(nu)beta(3)-antagonist (EMD 121974) were investigated in monolayers of a human intestinal cell line (Caco-2). Transepithelial transport was quantitated by reversed-phase high-performance liquid chromatography. Cytotoxic effects were characterized by determination of transepithelial electrical resistances (TEERs), propidium iodide (PI)-influx, FITC-phalloidin staining and the release of cytosolic lactate dehydrogenase (LDH). Medium chain fatty acids (MCFAs, NaC10, NaC12) and taurocholate (NaTC) were the most efficient enhancers of cyclopeptide and FITC-dextran 4400 permeability coefficients, displaying different time profiles of activity. Whereas NaTC (15 mM) showed almost a constant permeation enhancing effect from 20 min up to 120 min (ca. 12-fold), MCFA absorption enhancement was markedly dependent on incubation time (NaC10, 20 min: 1.2-fold, 120 min: 17-fold; NaC12, 20 min: 4.3-fold, 120 min: 13-fold). All cytotoxicity assays demonstrated that MCFAs were significantly more cytotoxic than NaTC. Ion pairing with hydrophobic amino acids and heptane sulfonate distinctly increased octanol-buffer partition coefficients of the cationic cyclopeptide but did not enhance its transepithelial permeability. Nanoparticles as well as beta-cyclodextrin neither affected integrity of the cells nor transport properties of the cyclopeptide. In summary, significant absorption enhancement was only observed with NaTC or MCFAs. Increase in permeability coefficients using NaTC occurred rapidly with acceptable cytotoxicities and merits further investigations.

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